

REMARKS/ARGUMENTS

Claims 37, 39-54, 56, 58, 59, and 61-67 are currently pending in this application. In order to advance prosecution and clarify claimed subject matter, claims 37, 39, 40 and 61 have been amended. Amendment to the claims find support throughout the specification as originally filed and specifically at, e.g., pages 3-4 and at page 12, lines 12-15 and lines 24-27; and page 13, lines 1-4. Claim 38 has been cancelled. Support for new claims 66 and 67 appears in, e.g., claim 37. Applicants assert the right to reclaim withdrawn or cancelled subject matter in co-pending applications. No new matter has been added.

Rejections under §103(a)

Claims 37-59 were rejected under 35 U.S.C. §103(a) as being unpatentable over Wagner (WO 00/04382), "Wagner" in view of Kolster. The Applicants respectfully traverse this rejection.

The application relates *inter alia* to a sensitive label free detection system wherein an enzyme may be specifically immobilized on an array compatible with MALDI, while conserving the enzyme's functional activity and performing a reaction directly on the MALDI probe followed by detecting a change in the reactants/substrate or product. Immobilizing proteins in a specific manner and detecting enzymatic catalysis directly on a mass spectrometry probe is an important and significant advancement over the prior art. Previously, such reactions were performed off-line and the products of the reaction transferred to a MALDI probe.

There is no motivation to combine the teachings of Wagner and Kolster in order to arrive at the instant invention. As is explained by the Federal Circuit, the motivation to combine is part of the discussion in determining the scope and content of the prior art.² Thus, where all claim

² DyStar Textilfarben GmbH & Co. Deutschland KG v. C.H. Patrick Co., 464 F.3d 1356, 1360, 80 USPQ2d 1641, 1645 (Fed. Cir. 2006); *citing* SIBIA Neurosciences, Inc. v. Cadus Pharma, Corp., 225 F.3d 1349, 1356 (Fed. Cir. 2000).

limitations are found in a number of references, the fact finder must determine "[w]hat the prior art teaches... and whether it motivates a combination of teachings from different references".³

Wagner relates to the immobilization of proteins on a substrate and detection of binding events only, such as, for example, antibody binding to epitopes and binding events associated with protein-protein interactions. Although Wagner refers to non-label methods of protein binding detection, the substrate, presentation of the samples and the detection methods described in Wagner are not compatible with MALDI or mass spectrometry in general. Rather, Wagner focuses on optical detection methods (pages 45-47). Therefore, the person of ordinary skill in the art would not modify Wagner to arrive at the claimed invention. In short, Wagner does not teach or suggest the claimed method of detecting enzymatic activity wherein an enzyme may be specifically immobilized on an array compatible with MALDI, while conserving the enzyme's functional activity and performing a reaction directly on the MALDI probe followed by detecting a change in the reactants/substrate or product using mass spectrometry.

Kolster does not remedy the deficiencies of Wagner. Kolster relates to standard MALDI for use in DNA diagnostics and does not teach or suggest detection of enzymatic activity. At best, Kolster relates to methods providing for increased accuracy and reliability of nucleic acid detection by mass spectrometry. However, Kolster does not mention or suggest a method of detecting enzymatic activity wherein an enzyme is specifically immobilized on an array compatible with MALDI, while conserving the enzyme's functional activity, and performing a reaction directly on the MALDI probe followed by detecting a change in the reactants/substrate or product.

Thus, one of ordinary skill in the art would not be motivated to look to the teachings of Wagner and Kolster to elucidate the instant methods. For the above reasons, Applicants respectfully request that the obviousness rejection be withdrawn.

³ *Id.* citing In re Fulton, 391 F.3d 1195, 1199-1200 (Fed. Cir. 2004).

Rejections under §112, 1st paragraph

35 U.S.C. §112, First Paragraph – Enablement

Claims 37-59 have been rejected under 35 U.S.C. §112, first paragraph, for lack of enablement. The Examiner states that the specification while being enabling for polyethylene glycol bound with a poly amino acid, does not reasonably provide enablement for a layer resistant to non-specific protein binding comprising protein repellent molecules. *Id.* Applicants traverse the rejections in view of the remarks presented herein and amendments to the claims.

The test for enablement is whether one reasonably skilled in the art could make or use the claimed invention without undue experimentation, based on the disclosure in the application and the information available in the art. *United States v. Teletronics, Inc.*, 857 F.2d 778, 785 (Fed. Cir. 1988); MPEP § 2164.01. The Office must consider many factors for enablement, including the quantity of experimentation necessary, the amount of direction or guidance presented, the presence or absence of working examples, the nature of the invention, the state of the prior art, the relative skill of those in that art, the predictability or unpredictability of the art, and the breadth of the claims. *In re Wands*, 858 F.2d 731, 737 (Fed. Cir. 1988); MPEP § 2164.01(a).

Applicants respectfully point to the significant guidance and working examples provided in the instant case. The instant application clearly provides enablement for other protein-repellant surfaces, for example at paragraph [0060] of the U.S. Application 2006/0275855:

The component molecules responsible for repelling non specific proteins include molecules which are generally hydrophilic in nature. They include polymers, such as, for example, polyethylene glycol, dextran, polyurethane and polyacrylamide and self assembled monolayers (SAM). Preferably the polymers comprise one or more functional side groups via which the protein capturing moieties can be attached. In the case of polyethylene glycol the functional group is a hydroxyl group. The molecules responsible for repelling non specific proteins may be bound directly to the surface as in, for example the case of SAM's or they may be attached via a linker. Particularly preferred as linkers are poly amino acids such as, for example, poly L lysine, poly L aspartic acid, poly L glutamic acid or mixtures thereof.

Thus, the instant application provides sufficient guidance and working examples to show how to use protein-repellant surfaces. *See, e.g.*, MPEP §§2164.01(b), (c), and 2164.02.

In addition, the claims have been amended to include the feature that enzyme binding moieties are incorporated into the layer and so the enablement objection in this regard is moot.

Notably, the test for “undue experimentation” is not merely quantitative, and the time and difficulty of experimentation are not determinative. *Wands*, 858 F.2d at 737; MPEP §2164.06. A considerable amount of experimentation is permissible if it is merely routine or if the specification provides a reasonable amount of guidance for how the experimentation should proceed. *Wands*, 858 F.2d at 737; MPEP §2164.06. Where an invention involves biological activity, this itself does not constitute “undue experimentation,” particularly where the level of skill is high (as noted in the instant case; *see* Office Action, page 7). *Wands*, 858 F.2d at 740. Furthermore, Applicants need only provide *sufficient* disclosure to teach those of skill in the art how to make and use the claimed invention. MPEP § 2164. The standard does not require thousands of examples or every possible species for the claimed invention. *In re Angstadt*, 190 U.S.P.Q. 214, 218 (C.C.P.A. 1976).

Consequently, based on the knowledge of those skilled in the art at the time of filing, together with the disclosure provided in the instant specification, Applicants respectfully submit that amended claims satisfy the enablement requirement. Applicants request reconsideration and withdrawal of the rejection.

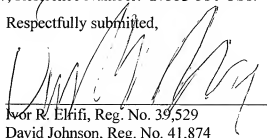
Rejections under § 112, second paragraph.

Claims 37-54, 56-59, 61-65 were rejected under 35 U.S.C. §112, 2nd paragraph as allegedly being indefinite. In view of the amendments to claims 37, 39, 40, 56 and 61 and cancellation of claim 38, Applicants urge that this rejection is moot and should be withdrawn.

Please charge any additional fees, or credit any overpayment of same, to Deposit Account
Number: **50-0311**, Customer Number: **35437**, Reference Number: **27353-514-US1**.

Respectfully submitted,

Dated: August 3, 2009



For R. Elrifi, Reg. No. 39,529
David Johnson, Reg. No. 41,874
Attorneys/Agent for Applicants
c/o MINTZ, LEVIN
One Financial Center
Boston, MA 02111
ph 617 542-6000